5U), bardoxolone methyl (CDDO-Me) (Najjar and Finke, 2013), or (c) functionally inhibit MDSC (phosphodiesterase type 5 (PDE-5) inhibitors, cyclooxygenase 2 (COX-2) inhibitors) (Najjar and Finke, 2013).

Gemcitabine (GEM, Gemzar), fluorouracil (f-5U) and other FDA-approved chemotherapeutic agents that are used for the treatment of a variety of cancers in the clinical arena, were found to selectively reduce the content of MDSC in both tumor-bearing mice and humans (Le et al., 2009; Suzuki et al., 2005; Vincent et al., 2010). However, despite a delay in cancer progression, none of these drugs was found to significantly increase time to metastases and patients survival (e.g. in treatment of pancreatic cancer).

Photodynamic therapy (PDT) in general and vascular-targeted PDT (VTP) in particular using novel bacteriochlorophyll derivatives (hereinafter Bchl-D) were shown to selectively ablate localized solid tumors in different targets (WO 00/33833; WO 2004/045492). In particular, VTP with the Bchl-D designated WST11, after successful clinical trials (Azzouzi et al., 2013, 2017; Eymerit-Morin et al., 2013), has been recently approved for use in early stage prostate cancer treatment.

Metronomic chemotherapy, which was originally designed to inhibit angiogenesis, involves low-dose chemotherapeutic agents administered in a frequent regular schedule with no prolonged breaks and minimizes severe toxicities (Ge et al., 2012; Ghiringhelli et al., 2007). Such treatments were found to particularly impact pro tumor immune cells proliferation in a specific cell population manner.

SUMMARY

In one aspect of the present disclosure, there is provided a use of an anti-myeloid-derived suppressor cells agent ("anti-MDSCs agent") for the manufacture of a medicament for the treatment of a primary cancer solid tumor or a metastasis thereof, wherein the medicament is to be administered sequentially with an anionic bacteriochlorophyll derivative (“Bchl-D) optionally conjugated with an RGD-containing peptide or RGD-peptidomimetic residue, and the administration of the Bchl-D is to be followed by photodynamic therapy (PDT)

wherein

said anti-MDSCs agent is gemcitabine that is to be administered in a dose lower than its conventional dose in monochemotherapy, once before the administration of the

Bchl-D and several times, at determined time intervals of 5 to 10 days or more, after said PDT;

said anti-MDSC agent is to be administered from 4 to 10 times or more; and

an interval between two such determined intervals may be longer than each determined interval.

The present disclosure also provides an anti-myeloid-derived suppressor cells agent (hereinafter "anti-MDSCs agent") and a bacteriochlorophyll derivative (hereinafter “Bchl-D) for use in combination therapy for cancer, wherein the anti-MDSC agent and the Bchl-D are administered sequentially and the administration of the Bchl-D is followed by photodynamic therapy (PDT).

The present disclosure further provides a method for treatment of cancer by combination therapy comprising administering to a patient in need thereof: (i) a therapeutically effective amount of an anti-myeloid-derived suppressor cells (MDSCs) agent (hereinafter "anti-MDSCs agent"); and (ii) a therapeutically effective amount of a

CLAIMS

1. Use of an anti-myeloid-derived suppressor cells agent ("anti-MDSCs agent") for the manufacture of a medicament for the treatment of a primary cancer solid tumor or a metastasis thereof, wherein the medicament is to be administered sequentially with an anionic bacteriochlorophyll derivative (“Bchl-D), optionally conjugated with an RGD-containing peptide or RGD-peptidomimetic residue, and the administration of the Bchl-D is to be followed by photodynamic therapy (PDT),

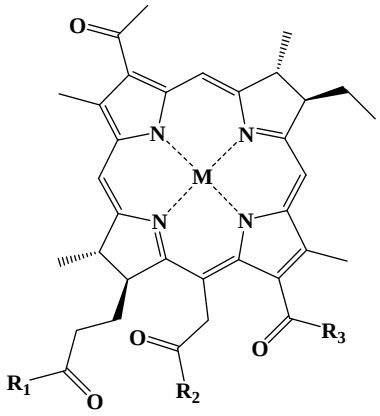
wherein

said anti-MDSCs agent is gemcitabine that is to be administered in a dose lower than its conventional dose in monochemotherapy, once before the administration of the Bchl-D and several times, at determined time intervals of 5 to 10 days or more, after said PDT;

said anti-MDSC agent is to be administered from 4 to 10 times or more; and

an interval between two such determined intervals may be longer than each determined interval.

2. The use according to claim 1, wherein the anionic Bchl-D has the formula I:



(I)

wherein

M represents 2H or Pd;

R_1 is O-R_4 or -NHR_5, wherein R_4 is H, H^+, an ammonium group or a monovalent metal cation selected from Na^+ and K^+, and R_5 is an RGD-containing peptide or RGD peptidomimetic residue;

R_2 is –O-C_1-C_6 alkyl, preferably –O-methyl;

R_3 is -NH-$(CH_2)_n$-SO_3^- R_6^+, wherein n is 2 or 3 and R_6^+ is a monovalent metal cation selected from Na^+ and K^+; and

pharmaceutically acceptable salts and optical isomers thereof.

3. The use according to claim 2, wherein the anionic Bchl-D of formula I is not conjugated to an RGD-containing peptide or RGD peptidomimetic residue.

4. The use according to claim 3, wherein the anionic Bchl-D of formula I is the Bchl-D herein designated WST11 or the Bchl-D herein designated STL-7012.

5. The use according to claim 3 or 4, wherein the administration of the Bchl-D is to be followed by vascular-targeted PDT (VTP) and the area to be treated is to be illuminated 0-30 min after the administration of the Bchl-D is completed.

6. The use according to claim 2, wherein the anionic Bchl-D of formula I is conjugated to an RGD-containing peptide or RGD peptidomimetic residue.

7. The use according to claim 6, wherein the anionic Bchl-D of formula I is conjugated to a cyclic RGD-containing peptide, and the conjugated Bchl-D is selected from the Bchl-Ds herein designated STL-6014, STL-6033, STL-6038, and STL-6068.

8. The use according to claim 6 or 7, wherein the administration of the Bchl-D is to be followed by tissue-directed PDT and the localized solid tumor to be treated is to be illuminated at least 4h, preferably 6 h, after the conjugated Bchl-D is administered.

9. The use according to claim 1, wherein the Bchl-D is to be administered a sole time, and the administration of the Bchl-D is to be followed by PDT.

10. The use according to claim 9, wherein the Bchl-D is STL-6014, and the administration of the Bchl-D is to be followed by PDT.

11. The use according to claim 10, wherein the localized solid tumor to be treated is illuminated at least 4h after the Bchl-D is administered.

12. The use according to claim 9, wherein the Bchl-D is WST11, and the administration of the Bchl-D is to be followed by VTP.

13. The use according to claim 12, wherein the area to be treated is illuminated 0-30 min after the administration of the Bchl-D is completed.

14. The use according to any one of claims 1 to 13, wherein the anti-MDSC agent is to be administered in a dose 3 or 4 times lower than the conventional dose of the agent in conventional monochemotherapy.

15. The use according to any one of claims 1 to 14, wherein said primary cancer solid tumor is melanoma, renal cell carcinoma,

colon, breast, lung, prostate, bladder, brain, pancreas, or head and neck tumor.